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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/420,692	10/19/1999	JEFFREY M. BESTERMAN	106.101.197	3139

32254 7590 07/16/2003

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EXAMINER
EPPS, JANET L

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/420,692	BESTERMAN ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6 and 11-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6 and 11-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

2. Claim 3 is objected to because of the following informalities: Claim 3, line 4, recites the limitation "methytransferaseand." This limitation was likely the result of a typographical error, it is likely that Applicants intended claim 3, line 4, to recite "methyltransferase and." Appropriate correction is required.

Response to Amendment

3. The Declaration under 37 CFR 1.132 filed 5-06-03 is insufficient to overcome the rejection of claims 1-3, 6, and 11-34 based upon 35 USC 112, 1st paragraph as set forth in the last Office action because the facts presented are not germane to the rejection at issue, and the showing is not commensurate in scope with the claims. The instant claims are directed to a combinatorial method for treating for a disease responsive to inhibition of a human DNA methyltransferase. However, the facts presented in the Declaration are directed to the use of the DNA MeTase inhibitor MG98, and does not address the co-administration of an antisense oligonucleotide with a protein effector of human DNA methyltransferase. It is noted that the Declaration does not even address the methods recited in the instant application since the Declaration was originally directed to a different application, in particular application 08/652,425, having a different inventor.

Response to Arguments

Claim Rejections - 35 USC § 112

4. Claims 1-3, 6, 11-34 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the expression of a gene in a cell *in vitro* and in xenograft tumor cells in an experimental mouse model *in vivo* does not reasonably provide enablement for inhibiting the expression of a gene *in vivo* for the therapeutic treatment of mammals broadly, an in particular a human, having a disease associated with the expression of said gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record set forth in the Official Action mailed 5-08-02.

5. Applicant's arguments filed 1-15-03 and 5-06-03 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the teachings of issued US Patents 6,066,625 and 6,184,211 provide sufficient enablement to enable the full scope of the claimed invention. However, neither reference provides sufficient guidance for the co-administration of an antisense oligonucleotide targeting DNA MeTase and an protein effector, wherein said co-administration results in a synergistic interaction, thereby producing treatment effects for diseases responsive to inhibition of a human DNA MeTase.

Moreover, the disclosure of 6,066,625 teaches away from the use of the protein effector 5-aza-cytidine as recited in, for example, claim 6 of the instant application. See for example, col. 2, lines 9-16, that states: "[H]owever, 5-azaC is a nucleoside analog that has multiple effects on cellular mechanisms other than DNA methylation, thus making it difficult to interpret data obtained from these studies. Similarly, 5-azadC forms a mechanism based inhibitor upon

integration into DNA, but it can cause trapping of DNA methyltransferase (hereinafter, DNA MeTase) molecules on the DNA, resulting in toxicities that may obscure data interpretation." Therefore, since the disclosure of this patent teaches toxicities associated with 5-aza-cytidine, it is unclear how the disclosure of this patent can be used to support the enablement of a combination therapy that comprises the administration of 5-aza-cytidine with antisense targeting DNA MeTase. Moreover, as stated above, the Declaration provided by Applicants is not commensurate in scope with the claimed invention. The Declaration addresses the use of a single specific DNA MeTase inhibitor in a human, it is evident that the specification as filed, which provides *in vivo* mouse studies, does not provide sufficient guidance to produce the results set forth in the Declaration which involves the treatment of a human. Moreover, the Declaration does not describe the co-administration of antisense oligonucleotides with a DNA MeTase protein effector, as encompassed by the instantly claimed methods.

Finally, the instant claims are not limited to any particular antisense oligonucleotide sequence, therefore the claims encompass the administration of any antisense oligonucleotide targeting DNA MeTAse, in combination with a protein effector. Although, the prior art may enable the in vivo use of MG98, the results obtained using that particular inhibitor can not be extrapolated in order to predict the behavior of all antisense inhibitors of DNA MeTase *in vivo*. As stated in the prior Office Action, the behavior of an antisense oligonucleotide in a cellular environment is unpredictable according to the teachings of Crooke (1998). Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, and sequence of oligonucleotide and cell type. The influence of non-antisense effects, for example phosphorothioate oligonucleotides

tend to bind non-specifically to many proteins, wherein such protein binding influences cellular uptake, distribution, metabolism and excretion of said oligonucleotide. Additionally, non-specific protein binding may produce effects that can be mistakenly interpreted as antisense activity, and may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may non-specifically interact with other biological molecules, such as lipids, or carbohydrates, wherein the chemical class of oligonucleotide will influence such interactions studied (Crooke, 1998; p. 3). Since Crooke clearly teaches that there are a significant number of factors that influence the behavior of antisense based, compounds in a cell, one of skill in the art would not accept on its face that the data supporting the use of MG98 would be necessarily predictive of the use of other antisense compounds targeting DNA MeTase, and further with the co-administration of a protein effector.

Applicant's arguments do not take the place of evidence, the instant claims remain rejected for the reasons of record.

6. Claims 1-3, 6, 11-34 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record in the Official Action mailed. 5-8-02.

Applicant's arguments filed 1-15-03 and 5-06-03 have been fully considered but they are not persuasive. Applicants traverse the instant rejection by amending claims 1-3 to recite "human DNA methyltransferase." Furthermore, Applicants traverse the instant rejection on the

grounds that contrary to the statement of Dr. Branch, a large number of oligonucleotides would not have to be screened to find out which ones work, and that it is not necessary to show all antisense oligonucleotides that work in order to show one of skill in the art that the inventors possessed the claimed method at the time of filing. However, contrary to Applicant's assertions, first it is noted that Applicants have not provided a specific structural description of the human DNA methyltransferase recited in the instant claims. Although the specification as filed provides a GenBank Accession number for one form of human DNA MeTase, the instant claims encompass antisense oligonucleotides targeting polymorphic, allelic, mutated, and splice variants of the DNA MeTase gene isolated from humans. Moreover, antisense oligonucleotides targeting one form of human DNA MeTase cannot be used to predict the structures of other functional antisense molecules targeting other forms of human DNA MeTase, since structurally distinct coding sequences would produce unique mRNA folding patterns, and thereby producing unique antisense accessible target regions, see Branch (1998).

Contrary to Applicant's assertion that the teachings of Dr. Branch were incorrect, and that a large number of oligonucleotides would not have to be screened to find functional ones, the teachings of Branch correctly state that "RNAs are complex molecules with intricate internal structures...[r]ecent studies emphasize the extent to which native RNA structure restricts the binding of ODNs *[oligonucleotides]*....[t]hey found that 'surprisingly few' ODNs bound stably to the mRNA, and concluded that binding is probably 'confined to those regions in the RNA which provide an accessible substructure.'" (page 49, col. 1, paragraphs 2-3). Therefore, because each structurally distinct antisense oligonucleotide would be expected to interact with its target mRNA in a distinct manner, and would be expected to have varying degrees of inhibitory

activity if any at all. Moreover, Branch (1998) correctly states that "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells." (page 49, col. 1, paragraph 3). Since the state of the antisense art indicates the necessity for empirical studies in order to determine effective antisense compounds, one of skill in the art would not accept on its face that antisense oligonucleotides effective to inhibit the expression of one mRNA target, would be effective to inhibit the expression of all polymorphic, allelic, mutated and splice variants of said mRNA target.

In regards to the protein effectors, Applicant's have not addressed how teachings of the specification as filed can be used to predict the structures of all protein effectors targeting human DNA methyltransferase that are encompassed by the instant claims.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Fri, 8:30AM-6: 30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
July 10, 2003

Karen A. Lacourciere
KAREN LACOURCIERE
PATENT EXAMINER